employed to assay plasma MAO activity.

EEG "Driving" Responses to Photic Stimulation

Two EEGs will be taken, one on the day of the fourth and one on the day of the fifth MAO blood sample to provide for adaptation to the EEG procedure. A third critical EEG will be taken on another day, after 3 hours of abstinence from smoking.

The EEGs will be obtained with a Grass model 5P5 electroencephalograph preamplifier. Bipolar occipital electrodes will be placed 2.5 cm to either side of the midline and between and parallel to the lines formed between the O_1-O_2 and P_3-P_4 derivations in the international 10-20 system of electrode placement. These electrodes are used to record the EEG responses to each of 18 photic stimulation trials. A Grass PS2 photic stimulator will be employed. The stimulation trials each last 10 seconds and are spaced 10-20 seconds apart, and are at 5, 10, 15, 20, 25 and 30 flickers/second. Each of these frequencies are administered at steps 2, 4 and 8 of the Grass intensity scale.

The EEG driving response is defined as the evocation of EEG waves at the fundamental or harmonic frequency of the photic stimulation for one full second, with no other EEG wave being visually detectable during that time.

The EEG driving response is scored as either present or absent for each stimulation trial. The EEGs will be independently scored by two scorers. Interscorer reliability in the past has been in the vicinity of .95.

Performance of Automatized Tasks

Automatization performances will be assessed by the method described in Klaiber, et al., (1967).

Anthropometric Indices of Testosterone Stimulation

Pubic hair development, and chest and biceps circumferences are each known to be affected by testosterone stimulation (Dorfman and Shipley); hence each will be employed as an index of endogenous testosterone stimulation.

The pubic hair ratings are made from photographs, with non-relevant portions of the picture eliminated, on a 5 point scale similar to that described by Tanner (1962).

The three anthropometric indices will be combined in the manner described by Klaiber et al., (1967).

Free and Total Plasma Testosterone and Serum LH and FSH

A blood sample for measurement of free and total plasma testosterone and for serum LH and FSH will be obtained on the day of the third plasma MAO blood sampling. The free and total testosterone will be measured by the method of Rosenfield (1971). The LH and FSH will be measured by the method of Odell (1967).

Study II

This is a manipulative study which examines the effects of smoking one cigarette on frequency of EEG "driving" responses. The cigarette would be smoked immediately after completion of the third, critical EEG trial of Study I. Another EEG trial will then be immediately obtained to allow comparison and with the preceding pre-smoking EEG trial.

This procedure, i.e., two EEG trials within a short span of time, will be repeated on a later day without a cigarette interspersed between trials to control for the possibility that any main effect change in the second trial is due to some other factor, such as occipital neural satiation.

Subjects:

The same subjects as in Study I will be employed.

Cigarette:

A standard cigarette will be employed. Subjects will be requested to inhale. Non-smokers will be instructed, if necessary, how to inhale.

Future Work

The studies proposed here should logically be extended in various ways in the future. Measurement of blood testosterone metabolic clearance and production rates would be most important. These measures reflect the physiologic activity of testosterone more acurately than do blood testosterone levels.

The differences in adrenergic functioning believed to exist between male smokers and non-smokers should be investigated in females.

The psychophysiologic factors differentiating smokers and non-smokers may allow for prediction of future smoking behavior in young adolescents. This endeavor would require a longitudinal study across puberty. A longitudinal study of hormonal, psychological and physical changes occuring across puberty is currently being planned for our laboratory, and a smoking behavior study could easily be incorporated into this work.

Since prostaglandins appear to modulate norepinephrine release in the adrenergic nervous system, it would be important to assess differences in PG levels in smokers and non-smokers. The concentration of PGs is higher in seminal fluid than in any other type of tissue. Therefore, measurements should be made of seminal fluid PG E and F levels in smokers and non-smokers. We are currently carrying out a study on seminal fluid PG levels and the type of study discussed could be easily incorporated into this ongoing research.

10. Space and Facilities Available

The proposed research will be carried out in the laboratories of the Worcester Foundation for Experimental Biology and of Worcester State Hospital.

A fully equipped endocrine clinic is available at the Worcester Foundation. The assays for plasma MAO activity, total and free plasma testosterone, and serum LH and FSH are currently operative in the clinic laboratories.

The Psychology Department of Worcester State Hospital has a functioning research EEG laboratory with photic stimulation equipment. Cognitive testing facilities are also available in the Psychology Department.

All of the proposed procedures are currently being performed for other projects.

11. Additional Facilities required

None

heroin.

The anthropometric data, e.g., low pubic hair ratings, suggests that testosterone activity is reduced in these individuals. A low level of testosterone activity could account for their elevated MAO activity which, in turn, could result in poor central adrenergic functioning. It is our hypothesis that the drugs that these addicts have used, such as heroin and marijuana, stimulate CNS adrenergic functioning and thereby momentarily relieve the negative symptoms associated with deficient CNS adrenergic functioning. This initial study has formed the basis of a research proposal submitted to the U.S.P.H.S.

Central Adrenergic Functioning and Cigarette Smoking

A second pilot study of our hypothesis that impaired central adrenergic functions are associated with addictive tendencies involving cigarette smoking.

Twenty-four subjects, half smokers (1 pack a day or more); half non-smokers; half male; half female; were compared on rates of EEG "driving". Two such trials were obtained, one at least 3 hours after the last cigarette smoked by the smokers; and another trial immediately following the smoking (inhalation required) of one cigarette.

Our results indicate that the smokers have greater rates of EEG driving than non-smokers ($p<.001$); and that smoking one cigarette significantly reduces this rate of EEG driving in all subjects ($p<.001$). Figure 1 portrays these results. The reduction in EEG driving associated with cigarette smoking is probably a direct result of the CNS adrenergic stimulating action of nicotine. Once again, as in the drug addict, addictive individuals, i.e., cigarette smokers, have evidence of adrenergic insufficiency. The smoking condition also indicates that the adrenergic insufficiency tends to be alleviated by cigarette smoking.

Other studies have also demonstrated EEG differences between smokers and non-smokers, (Hauser et al., 1958; Brown, 1973, 1968). Those studies, however, lacked a theoretical orientation within which to interpret the observed relationships. The results of the present study, on the other hand, conform to the expectations derived from our theoretical model involving central adrenergic functioning.

The above pilot study was based on a relatively small number of subjects. We propose to repeat that study, and add additional measures in order to meet the following specific aims.

Specific Aims

Study I

1) To assess the frequency of EEG "driving" responses to photic stimulation of smokers and non-smokers in a larger homogeneous sample of subjects, i.e., 21 to 30 year old males.

2) To assess the plasma MAO activity of the above smoking and non-smoking samples.

3) To assess performances of automatized tasks of the smokers and non-smokers

4) To assess plasma total and free testosterone levels and serum LH and FSH in the above samples.

5) To assess anthropometric indices of testosterone stimulation in the above samples.

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(continued)

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14. First year budget:

A. Salaries (give names or state "to be recruited") Professional (give % time of investigator(s) even if no salary requested)	% time	Amount
Klaiber, Edward L., M.D., Principal Investigator	10%	$ 2,000
Cone, Frederick L., B.S., Senior Research Asst.	15%	2,000
Hawkins, Marion, R.N., Research Nurse	20%	2,000
Hall, Fernando, B.S., Research Assistant	25%	2,000
~~Technical~~ Consultants		
Vogel, William, Ph.D.	10%	2,000
Broverman, Donald, Ph.D.	10%	2,000
Sub-Total for A		12,000

B. Consumable supplies (by major categories)

Glassward, chemicals and Sundry	1,800
Sub-Total for B	1,800

C. Other expenses (itemize)

Subject costs	2,400
Fringe Benefit Charges on salaries at 18.5% (approx)	1,480
Sub-Total for C	3,880
Running Total of A + B + C	17,680

D. Permanent equipment (itemize)

Sub-Total for D	none
E	2,652
Total request	20,332

E. Indirect costs (15% of A+B+C)

O.K. LB

15. Estimated future requirements:

Depending on results obtained during the first year of study, an application for further support will be submitted in time for a January, 1976 continuation date. Further studies would be planned as outlined in the section on future work on page 9.

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(continued)

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estrogens acted to return both hypothalamic MAO activity (Kobayashi et al., 1966) and behavioral activity (Young add Fish, 1945) towards normal. In the human, amenorrheic women, who are known to be estrogen deficient (Brown et al., 1969), had abnormally elevated plasma MAO activity (Klaiber et al., 1971a) and heightened EEG driving response rates (Vogel et al., 1971); both of which could be returned to normal by the administration of oral conjugated estrogen.

Male endocrine patients requiring testosterone therapy were found, before treatment, to have elevated plasma MAO activity, which I.M. injections of testosterone returned towards normal (Klaiber et al., 1974). Anthropometric indices of testosterone stimulation, e.g., pubic hair development, chest and biceps circumferences, were found to be positively correlated with performances of automatization tasks (Klaiber et al., 1967). A 3 hour infusion of testosterone significantly enhanced performances of such tasks in normal men (Klaiber et al., 1971b); while injections of testosterone in endocrine patients enhanced both automatization performance and reduced their EEG driving response rates (Stenn et al., 1972).

Psychological Significance of Variations in Central Adrenergic Functioning

The central adrenergic functions have been postulated by Hess (1954) to be "ergotropic" i.e., they are believed to regulate such "work" activities of the brain as wakefulness, alertness, motor activity, sensory reactions, and to be associated with positive mood states. A deficit in central adrenergic functioning, on the other hand, has been postulated by Schildkraut (1964) to be the basis of mental depression whose symptoms include fatigue, apathy, reduced motor activity, and negative mood states. We have reported that depressed female patients have extremely high levels of plasma MAO activity and elevated levels of EEG driving, both of which could be corrected by the administration of oral conjugated estrogen (Klaiber et al., 1971a; 1974).

A Conceptual Model for Addiction

The above observations have led to the following conceptual model. Within the range of normal variation, individuals with relatively less gonadal steroid hormone stimulation tend to have relatively elevated MAO activity and reduced central adrenergic functioning. The negative psychological concomitants of reduced central adrenergic functioning, i.e., fatigue, depression, apathy, etc., then ensue. Such individuals will tend to be attracted to, and come to depend upon, any drug or substance which tends to momentarily alleviate these states, i.e., drugs that act as central adrenergic stimulants, at least in their short-term effects.

Central Adrenergic Functioning and Drug Addicts

Our first test of this hypothesis was a small sample (n=19) of male drug addicts using heroin and other drugs such as marijuana. Heroin is known to affect norepinephrine levels in the brain (Way and Shen, 1971) and marijuana has a predominantly adrenergic effect (Dagirmanjian & Byrd, 1962). The patients were studied while off all drugs. When matched by age with normal controls, the addicts had significantly elevated plasma MAO activity and significantly less pubic hair development. Chest and biceps circumferences were also smaller, but this could be due to the adverse diets that such individuals frequently have. Less ambiguous was the fact that over 40% (eight of the addicts) had histories of gonadal impairment (undescended testes; surgically removed testes; underdeveloped genitalia, etc.) that preceded their use of

Study II

1) To assess the effects of smoking one cigarette on EEG driving.

In the short time span of this smoking experiment, it is most unlikely that any significant change will occur in blood testosterone levels. Therefore, neither plasma testosterone nor plasma MAO activity will be measured after smoking one cigarette. Ideally, these assumptions should be empirically tested. However, they are eliminated in the present proposal in an effort to minimize costs.

8. Brief statement of working hypothesis:

The working hypotheses of this proposal are:

Study I

1) Smokers will evidence greater frequency of EEG "driving" responses to photic stimulation than non-smokers.

2) Smokers will have higher plasma MAO activity than non-smokers.

3) Male smokers will have less anthropometric evidence of testosterone stimulation than male non-smokers.

4) Male smokers will have lower free, but not necessarily lower total, plasma testosterone than non-smokers.

5) Smokers will perform automatized tasks less well than non-smokers.

Study II

1) Smoking one standard cigarette will acutely reduce the frequency of EEG "driving" responses in both smokers and non-smokers.

9. Details of experimental design and procedures

Method

Study I

This is a comparative study in which the dependent variables listed below are compared in smokers versus non-smokers.

Subjects

Thirty, 21 to 30 year old, male volunteer smokers (at least one pack a day); and thirty, 21 to 30 year old, male volunteer non-smokers matched for educational level. All subjects will be in good health and not using any other drugs or medications.

Dependent Variables

Plasma MAO Activity

Five blood samples, each at the same hour of different days, will be drawn to determine the average plasma MAO activity of each subject. The method of Otsuka and Kobayashi (1964) will be

While plasma and brain MAO activity may not be the same, we believe that the plasma MAO activity tends to reflect the state of brain MAO activity since both share, to a degree, a common biochemical environment. In support of these assumptions, we have noted that:

A) blood and brain MAO activity are positively correlated in their rate of recovery from an MAO inhibitor (Kobayashi and Kizuka, 1972);

B) in the rat, the jugular venous blood level of MAO activity averages 20% greater than that found in carotid arterial blood, indicating that the brain is one source of blood MAO activity (Kobayashi and Kizuka, 1973);

C) in humans, plasma MAO activity is significantly positively correlated with frequency of EEG "driving" responses to photic stimulation (Klaiber et al., 1971; Vogel et al., 1974); and significantly negatively correlated with performances of "automatization" tasks (Klaiber et al., 1967).

The question of the possible heterogeneous nature of monoamine oxidase has been a source of controversy. The evidence for the existence of multiple forms of MAO has been provided mainly by Sandler's group in England (Youdim and Sandler, 1967; Youdim et al., 1969; Youdim, 1973). Their position has been supported by other workers such as Shih and Eiderson (1973), Coquil et al. (1973), and Gomes et al. (1969). However, Hartman and Udenfriend (1972) have provided evidence to indicate the near-homogeneous nature of MAO based on immunological studies showing, for example, that the 3 MAO isoenzymes isolated by Gomes et al (1969) from beef liver were antigenically identical. In a recent study, Tipton, et al (1973) have shown that the multiple forms of MAO reported by Youdim et al. (1968, 1969, 1973) may be due to the binding of different amounts and/or types of lipid to a single enzyme species. When MAO was partly purified from human brain, that prepared according to the method of Youdim et al. (1968, 1969, 1973) separated into multiple bands whereas that prepared using perchlorate showed only a single band. On the basis of substrate specificities and response to enzyme inhibitors, Tipton et al. (1973) concluded that their findings were consistent with the contention that multiple forms of human MAO arise from differential binding of membrane material to a single enzyme species.

Although this question of the nature of MAO remains unresolved; it has little relevance to the MAO activity measurements of the blood. The plasma assay measures total MAO activity contained per unit volume, irrespective of enzyme origin or type. The amount of MAO activity in the plasma is minute and is probably not, itself, physiologically significant. However, as indicated above, it does appear to be a crude index of brain MAO activity.

Gonadal Steroid Hormones and Central Adrenergic Functioning

Our research has led us to believe that the gonadal steroid hormones, testosterone, estrogen and progesterone, significantly influence central adrenergic functions via their regulatory influence upon MAO activity.

Thus, hypothalamic MAO activity cycles with estrus cycle in the rat (Kamberi and Kobayashi, 1970); and plasma MAO activity cycles with menstrual cycle in humans (Klaiber et al., 1971). In the rat, ovariectomy resulted in elevated hypothalamic MAO activity (Kobayashi et al. 1966); and diminished behavioral activity (Wang, 1923; Richter, 1927); while the administration of

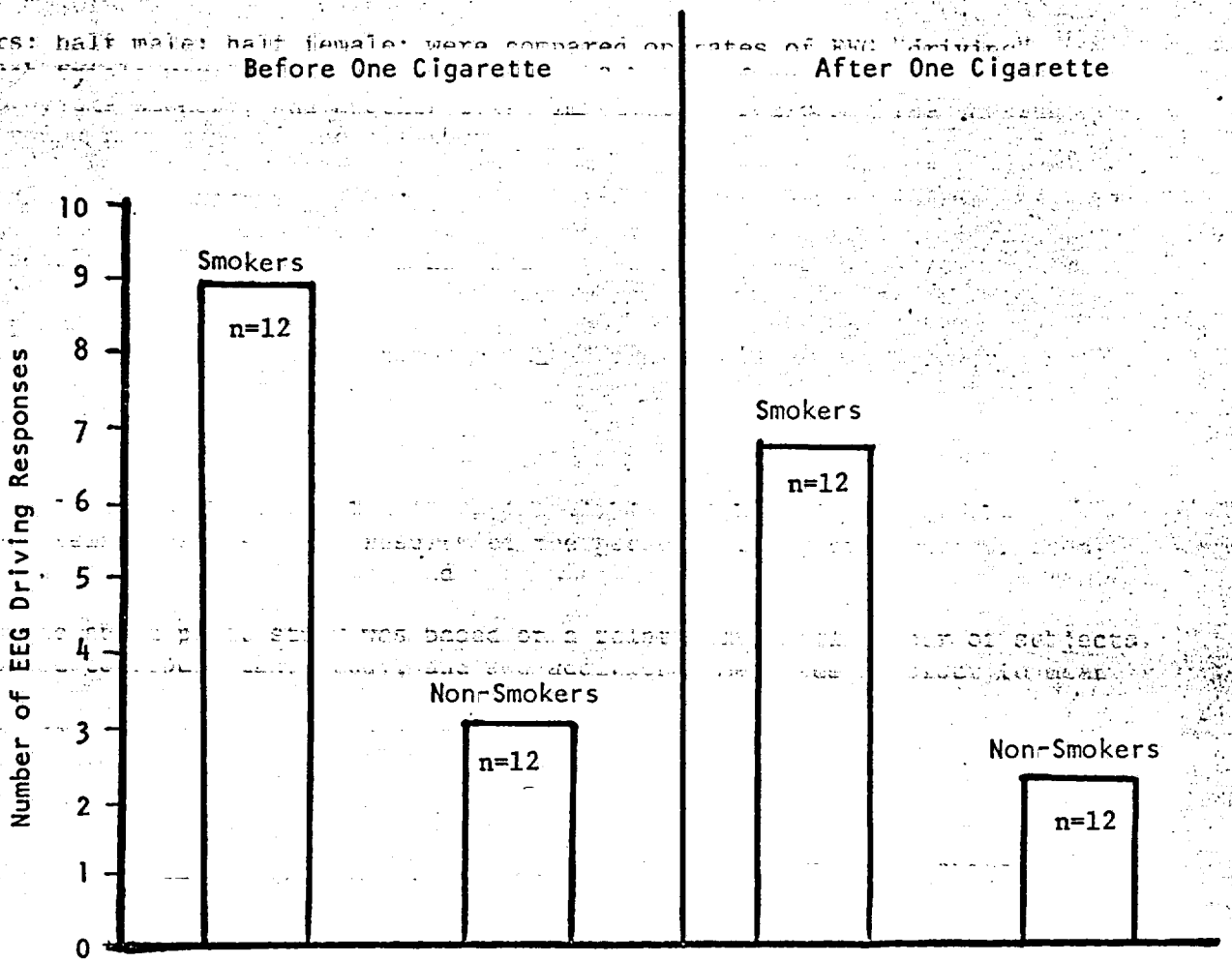

Figure 1

EEG Driving Responses in Smokers and Non-Smokers,

Before and After One Cigarette

#1003

THE COUNCIL FOR TOBACCO RESEARCH–U.S.A., INC.

110 EAST 59TH STREET
NEW YORK, N. Y. 10022
(212) 421-8885

Application for Research Grant
(Use extra pages as needed)

Date: July 30, 1974

1. Principal Investigator (give title and degrees):

Edward L. Klaiber, M.D. Senior Scientist

2. Institution & address:

The Worcester Foundation for Experimental Biology, Inc.
222 Maple Avenue
Shrewsbury, Massachusetts 01545

3. Department(s) where research will be done or collaboration provided:

Non-applicable

4. Short title of study:

Central Nervous System Adrenergic Functioning and Cigarette Smoking

5. Proposed starting date: January 1, 1975

6. Estimated time to complete: One year

7. Brief description of specific research aims:

Brief Rationale

The proposed research is based on the hypothesis that smokers tend to have impaired central adrenergic functioning compared to non-smokers. Impaired central adrenergic functioning has been associated with mental states of fatigue, apathy, reduced motor activity and negative mood states. Cigarette smoking is believed to act as a central adrenergic stimulant thereby alleviating these adverse states.

Impaired central adrenergic functioning may be, in part, secondary to insufficient gonadal hormone stimulation. The gonadal hormones are thought to influence central adrenergic functioning through their ability to inhibit monoamine oxidase (MAO) activity. This enzyme is important in the intra-neural regulation of monoamines that act as neurotransmitters in adrenergic neurons.

Specific Aims

The specific aims of the proposed research are that smokers, compared to non-smokers,

a) have relatively poor central adrenergic functioning as reflected by rate of EEG "driving" responses to photic

16. Other sources of financial support:

List financial support from all sources, including own institution, for this and related research projects.

CURRENTLY ACTIVE

Title of Project	Source (give grant numbers)	Amount	Inclusive Dates
Prostaglandins and other research for development of contraceptives	Agency for International Development Contract AID/csd-2837	$96,176	7/1/74 - 6/30/75

PENDING OR PLANNED

Title of Project	Source (give grant numbers)	Amount	Inclusive Dates
Mechanisms of Action of Gonadal Hormones in Depression	N.I.H. Research Grant MH 26145 - Approved But funding uncertain	$191,500	9/1/74 - 8/31/77
	N.I.H. Research Grant Unassigned - November 1974 Council	$183,300	1/1/75 - 12/31/77

It is understood that the investigator and institutional officers in applying for a grant have read and accept the Council's "Statement of Policy Containing Conditions and Terms Under Which Project Grants Are Made."

Principal investigator

Typed Name Edward L. Klaiber, M.D.

Signature Edward L Klaiber M.D. Date 7/30/74

Telephone 617 (Area Code) 757-7907 (Number) (Extension)

Checks payable to

Worcester Foundation for Experimental Biology, Inc.

Mailing address for checks

222 Maple Avenue

Shrewsbury, MA 01545

Responsible officer of institution

Typed Name Federico Welsch, M.D., Ph.D.

Title Associate Director

Signature F. Welsch Date 7/30/74

Telephone 617 (Area Code) 842-8921 (Number) 414 (Extension)

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stimulation; and by performances of "automatized" tasks. Both of these indices have been shown to be sensitive to adrenergic stimulants and blocking agents;

b) have relatively high levels of plasma monoamine oxidase (MAO) activity which act to impair central adrenergic functioning.

c) have relatively low levels of free plasma testosterone, and less anthropometric evidence of testosterone stimulation. Testosterone is believed to inhibit MAO activity thereby enhancing central adrenergic activity.

d) In addition, the proposed research would test the hypothesis that smoking a single cigarette will promptly affect the rate of EEG "driving" responses to photic stimulation in a manner similar to an adrenergic stimulant.

The bases for these hypotheses are described in detail below.

Introduction

This research group has been investigating aspects of central adrenergic functioning in humans for the past ten years, primarily in the context of mental depression, but also in relationship to individual differences in normal cognitive functioning, learning disabilities, and, most recently heroin addiction.

Our indices of central adrenergic functioning are:

1) Frequency of EEG "driving" responses to photic stimulation, i.e., the tendency of EEG rhythms to mimic the frequency of a bright flashing light. Adrenergic stimulants such as amphetamine (Shetty, 1971) and norepinephrine (Floru et al., 1962) tend to inhibit this response, while adrenergic blocking agents such as chlorpromazine (Killam et al., 1967) tend to augment the response.

2) Performances of overlearned repetitive "automatized" tasks. Examples of such automatization tasks are speeds of performance of simple addition problems, naming color hues, object naming, etc. These task performances are enhanced by adrenergic stimulants such as amphetamine and impaired by adrenergic blocking agents such as chlorpromazine (Broverman et al., 1968).

3) Plasma monoamine oxidase (MAO) activity. The MAO enzyme plays an important role in the intraneural regulation of monoamines that are believed to act as neurotransmitters in adrenergic nerves (Kopin, 1964).